Anti-carbonic anhydrase autoantibodies and serum beta-2 microglobulin correlate with the ClinESSDAI score in patients with Sjögren's syndrome

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An expert panel of the European League Against Rheumatism (EULAR) has developed and validated the EULAR Sjögren's syndrome activity index (ESSDAI) to evaluate the systemic symptoms of primary Sjögren's syndrome (pSS) (1). ClinESSDAI, a modification of the ESSDAI without its biological component, has recently been presented (2). ClinESSDAI is independent of B-cell biomarkers, and gives a slightly higher emphasis on constitutional, articular, pulmonary, renal and muscular symptoms than the ESSDAI, and was suggested to be better suited for clinical practice than the ESSDAI (2). The use of biological therapies in pSS is rapidly expanding (3-5), and therefore, reliable and easily applicable indicators of treatment response are of utmost importance.

We have previously applied the ESSDAI retrospectively to a well characterised cohort of pSS patients (6), and found that it correlated with serum beta-2 microglobulin levels and ESR (7). We now aimed to test the applicability of the new ClinESSDAI in this independent pSS patient cohort. As the ClinESSDAI itself does not include B-cell biomarkers, we aimed in particular to analyse its immunological correlations. To this end we determined the ClinESSDAI from the previously gathered (6) pSS patient cohort of 78 subjects (75 females and 3 males), aged 58±13 years, range 29–82 years, and mean duration of the disease 9±4 years. The study has been approved by the Ethics Committee of Tampere University Hospital, Tampere, Finland.

The mean ClinESSDAI (theoretical range from 0 to 135) was 11.50±8.20, ranging from 0 to 39, and corresponding well with the previously reported (7) mean ESSDAI of this cohort, which was 11.10±7.52. As in the EULAR cohort (2), the ClinESSDAI correlated significantly with the ESSDAI (r=0.987, $p<0.001$, Pearson correlation coefficient) also in this cohort, as well as with age and disease duration (Table I). Similar to our previous results on ESSDAI (7), the ClinESSDAI correlated with serum beta-2 microglobulin concentration, but not with serum IgG or complement C4 concentrations, or anti-SSA or anti-SSB antibody titers. The ClinESSDAI was significantly higher in patients in the highest (>2.9 mg/L) than in the lowest (<2.4 mg/L) tertiles of serum beta-2 microglobulin (15.58±9.34 *vs*. 10.77±7.11, $p=0.042$, *t*-test). There was a trend for a correlation between the ClinESSDAI and ESR, but unlike the findings with the ESSDAI (7), this correlation was not significant (Table I).

We have previously found an association between renal and respiratory manifestations and autoantibodies to several carbonic anhydrases (anti-CA) in patients with pSS (8-9). As renal and respiratory manifestations are given a rather high weight in the ClinESSDAI, we hypothesised that there might be a correlation between anti-CA autoantibodies and the ClinESSDAI. Interestingly, we found a slight but significant correlation between the ClinESSDAI and anti-CA VI, anti-CA VII and anti-CA XIII autoantibodies (Table I).

The levels of anti-CA VII autoantibodies have been found to be associated with urinary protein excretion and persistent dry cough in pSS patients (8-9), and anti-CA VI and anti-CA XIII autoantibodies with urinary pH (8). Serum beta-2 microglobulin levels in turn are associated with several extraglandular manifestations of pSS (6-7, 10). Both anti-CA autoantibodies and serum beta-2 microglobulin are thus signs of systemic inflammatory activity of pSS.

Serum beta-2 microglobulin and autoantibody production are dependent on B-cell activity. The ClinESSDAI was developed in part to avoid data collinearity in studies evaluating B-cell biomarkers. The correlation of anti-CA autoantibodies and serum beta-2 microglobulin with the ClinESSDAI gives support to the feasibility of the ClinESSDAI in biomarker and clinical studies and to its applicability in the follow-up of pSS patients in daily clinical practice.

Table I. Correlation (r) of the ClinESSDAI with clinical and immunological findings in 78 patients with primary Sjögren's syndrome (Pearson correlation coefficient).

Variable	r for ClinESSDAI	*p*-value
ESSDAI	0.987	<0.001
Age	0.224	0.048
Disease duration	0.255	0.024
ESR	0.210	0.065
Serum beta-2 microglobulin	0.382	0.001
Serum IgG	-0.078	0.495
Serum C3	-0.095	0.408
Serum C4	-0.078	0.495
ANA	-0.045	0.694
Anti-SSA antibodies, n=77	-0.118	0.308
Anti-SSB antibodies, n=77	-0.104	0.376
Anti-CA I antibodies, n=74	0.059	0.618
Anti-CA II antibodies, n=74	-0.039	0.739
Anti-CA VI antibodies, n=74	0.253	0.030
Anti-CA VII antibodies, n=74	0.281	0.015
Anti-CA XIII antibodies, n=74	0.262	0.024

ESSDAI: European League Against Rheumatism Sjögren's syndrome activity index; ANA: anti-nuclear antibodies; ESR: erythrocyte sedimentation rate; anti-CA antibodies: anti-carbonic anhydrase antibodies.

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